Reviewer: Gordon Cockell , Date February 12, 1999

STUDY TYPE: Subchronic Oral Toxicity, 3-Month Oral Toxicity Study in Rats (Administration in Food); OPPTS 870-3100 [§82-1]; OECD No. 408; 87/302 EEC, B.26

TEST MATERIAL (PURITY): CGA 293343 Technical (Thiamethoxam) 98.4%

SYNONYMS: 4H-1,3,5-Oxadiazin-4-imine,3-[(2-chloro-5-thiazolyl) methyl]tetrahydro-5-methyl-N-nitro-

CITATION: Bachmann M. (1996) 3-Month Oral Toxicity Study in Rats (Administration in Food). Ciba-Geigy Limited Short/Long-term Toxicology, Stein, Switzerland. CIBA Project No. 942089, January 23, 1996. Unpublished. MRID 44718703.

SPONSOR: Ciba-Geigy Limited Crop Protection Division, Basel, Switzerland.

EXECUTIVE SUMMARY: In a 3-month dietary toxicity study, CGA 293343 (98.4%) was administered to 10 Sprague-Dawley Tif:RAIf (SPF) rats/sex/dose in the diet at dose levels of 0, 25, 250, 1250, 2500 or 5000 ppm (0, 1.743/1.879, 17.64/19.19, 84.9/92.5, 167.8/182.1 or 328.8/359.1 mg/kg bw/day for males/females).

Treatment with CGA 293343 tech. did not affect the appearance and behaviour of the animals, mortality, food consumption, ophthalmology, hematology, urinalysis or gross pathology. Treatment resulted in reduced body weight and body weight gain in males at 1250 ppm and above, changes in clinical biochemical parameters including increases in creatinine, urea, cholesterol, and phosphate in males, decreased plasma glucose in males and marginal decreases in sodium and chloride levels in males and females at 1250 ppm and above. Increased liver, kidney, adrenal, heart and spleen weights relative to body weight were observed in high dose males, and decreased absolute heart and thymus weights were observed in high dose females. Increases in the incidence and occasionally the severity of microscopic lesions were observed in liver (including hepatocellular hypertrophy and lymphohistiocytic infiltration), kidney (including hyaline change in tubular epithelium in males, chronic tubular lesions in both sexes and nephrocalcinosis in females), spleen (hemosiderosis and extramedullary hematopoiesis) and adrenal gland (fatty change).

Treatment with CGA 293343 tech. in the diet for 3 months resulted in a **NOAEL of 25 ppm for males and 1250 ppm for females**, equal to mean daily intakes of **1.7 and 92.5 mg/kg body weight in males and females, respectively,** based on histopathologically observed changes in kidney (increased incidence of hyaline change in renal tubular epithelium and chronic tubular lesions in males at 250 ppm and increased incidence of chronic tubular lesions and severity of nephrocalcinosis in females at 2500 ppm). **The LOAEL is 250 ppm for males and 2500 ppm for females, equal to 17.6 and 182.1 mg/kg bw/day for males and females, respectively.**

This subchronic toxicity study is classified as acceptable and satisfies the guideline requirement for a subchronic oral study; OPPTS 87-3100 [§82-1]; OECD No. 408; 87/302 EEC, B.26 in the rat.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** CGA 293343 TECH
   Description: Light beige powder
   Lot/Batch #: KI 4654/18
   Purity: 98.4% a.i.
   CAS #: 153719-23-4

2. **Test animals: Species:** Rat
   Strain: Tif:RAIf (SPF) Sprague-Dawley
   Age and weight at study initiation: 6 weeks (5 weeks at delivery, followed by 7 day acclimation period), males 123.3-179.5 g, females 114.7-155.1 g (at week -1)
   Source: Animal Production, Ciba-Geigy Limited, Stein, Switzerland
   Housing: Individual, in Makrolon Type 3 cages
   Diet: Pelleted, certified standard diet (Nafag No. 8900), containing the appropriate concentrations of test material, available *ad libitum*
   Water: Tap water, available *ad libitum*
   Environmental conditions: **Temperature:** 22±2°C
   Humidity: 55±10%
   Air changes: 16-20 per hour
   Photoperiod: 12 hours light per day
   Acclimation period: 7 days

B. STUDY DESIGN:

1. **In life dates - start:** December 27, 1994 **end:** March 28-29, 1995

2. **Animal assignment**: Animals were assigned using computer-generated random numbers to the test groups in table 1.

TABLE 1: Study Design

Test Group	Conc. in Diet (ppm)	Dose to Animal (M/F) (mg/kg bw/day)	Male	Female
Control	0	0	10	10
Low	25	1.743/1.879	10	10
Low-mid	250	17.64/19.19	10	10
Mid	1250	84.9/92.5	10	10
High-mid	2500	167.8/182.1	10	10
High	5000	328.8/359.1	10	10

3. **Diet preparation and analysis**

Diet was prepared monthly by mixing appropriate amounts of test substance with certified standard pelleted diet (Nafag No. 8900) and was stored in stainless steel containers at room temperature. Analyses for homogeneity, stability and concentration of the test material in the diets were conducted using samples of diets prepared for treatment days 1-36 and 64-end. Samples for the stability test were stored at room temperature for 35 days, then deep frozen until analysis.

Results - Homogeneity Analysis: The homogeneity of the test diets ranged from -6% to +9% of the mean concentrations, for samples taken from the start, middle and end of discharge from the pelleting machine.

Stability Analysis: CGA 293343 technical was found to be stable in diets when stored at room temperature over a period of 35 days. After 35 days of storage at room temperature, concentrations ranged from 91.4% to 116.2% of nominal concentrations.

Concentration Analysis: The mean test material concentration in samples of diets from treatment day 1-36 were 104.6%, 104.5%, 100.8%, 95.8 and 94.2% of nominal concentrations for the 25, 250, 1250, 2500 and 5000 ppm dose groups, respectively. The mean test material concentration in samples of diets from treatment day 64 to the end of the study were 98.1%, 96.2%, 96.9%, 99.8 and 97.8% of nominal concentrations for the 25, 250, 1250, 2500 and 5000 ppm dose groups, respectively.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. **Statistics**: For each time point and parameter, univariate statistical analysis was performed. Non-parametric methods were applied to allow for normal and non-normal data distribution. Each treated group was compared to control using Lepage's two-sample test, and assessed for increasing or decreasing trend from control up to the respective dose group using Jonckheere's test for ordered alternatives. Two-sided asymptotic p-values were provided in the summary results, along with flags for significant differences between groups and increasing or decreasing trends in the treated groups. The default level of significance to flag results from both the Lepage and Jonckheere tests was $p<0.01$. The statistical methods used by the investigators are satisfactory.

C. **METHODS:**

1. **Observations**: Animals were inspected daily for signs of toxicity and mortality.

2. **Body weight**: Animals were weighed weekly.

3. **Food consumption and compound intake**: Food consumption for each animal was recorded weekly. Food consumption ratios were calculated by dividing weekly food consumption by midweek body weight and reported as g food/kg body weight/day. Actual test material intake values were calculated by multiplying the food consumption ratio by the nominal concentration of the test material in the diet (ppm) and dividing by 1000, resulting in a dose in mg/kg bw/day. An overall mean value was calculated based on nominal concentration in the diet, then this value was corrected for the analytically determined test material content in the food.

4. **Water consumption**: Water consumption was recorded weekly.

5. **Ophthalmoscopic examination**: All animals were examined prior to dosing and animals in the control and high dose groups were examined during week 13. Examination included observation of the eye appearance and of the periocular region, and detection of pupillary reflex using an ophthalmoscope. No treatment-related effects were noted, therefore no other animals were subject to ophthalmoscopic examination.

6. **Haematology & Clinical Chemistry:** Blood was collected following an overnight fast from all surviving animals of each dose group at the end of the treatment period. Blood was withdrawn from the orbital sinus using glass capillary tubes, for haematology and clinical analysis. The CHECKED (X) parameters were examined.

a. **Haematology**

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Haemoglobin (HGB)*	X	Large unstained cells
X	Leukocyte count (WBC)*	X	Mean corpuscular Haemoglobin (MCH)
X	Erythrocyte count (RBC)*	X	Mean corpuscular Haemoglobin concentration (MCHC)
X	Platelet count*	X	Mean corpuscular volume (MCV)
	Blood clotting measurements*		Reticulocyte count
	(Thromboplastin time)	X	Red cell distribution width (RDW)
	(Thromboplastin time)	X	Haemoglobin concentration distribution width (HDW)
	(Clotting time)	X	Methaemoglobin
X	(Prothrombin time)		

* *Required for subchronic studies based on Subdivision F Guidelines*

b. **Clinical Chemistry**

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
	Creatine phosphokinase	X	A/G ratio
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (also SGPT)*		
X	Serum aspartate amino-transferase (also SGOT)*		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

7. **Urinalysis***

Urine was collected from all surviving animals of each dose group following an overnight fast, at the end of the treatment period. The CHECKED (X) parameters were examined.

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

* Not required for subchronic studies

8. Sacrifice and Pathology

All animals were subjected to gross pathological examination and the CHECKED (X) tissues were collected and preserved for possible histopathological examination. The tissues marked (E) were subject to microscopic examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT	X	NEUROLOGIC
X	Tongue	EX	Aorta*	EXX	Brain*
X	Muzzle	EXX	Heart*	EX	Peripheral nerve*
EX	Salivary glands*	X	Sternum with bone marrow*	X	Spinal cord (3 levels)^{T}
EX	Esophagus*	EX	Lymph nodes*	EX	Pituitary*
EX	Stomach*		(mesenteric/axillary)	X	Eyes (optic n.)^{T}
EX	Duodenum*	EXX	Spleen*		
EX	Jejunum*	EXX	Thymus*		GLANDULAR
EX	Ileum*			EXX	Adrenal gland*
EX	Cecum*		UROGENITAL	X	Extraorbital Lacrimal gland^{T}
EX	Colon*	EXX	Kidneys*$^{+}$	X	Orbital gland
EX	Rectum*	EX	Urinary bladder*	X	Zymbal gland
EXX	Liver*$^{+}$	EXX	Testes*$^{+}$	X	Mammary gland^{T}
	Gall bladder*	EX	Epididymides	EXX	Thyroid with Parathyroids*$^{++}$
EX	Pancreas*	X	Prostate		
		X	Seminal vesicle		OTHER
	RESPIRATORY	EXX	Ovaries	EX	Bone (femur with joint)
EX	Trachea*	EX	Uterus*	X	Skeletal muscle
EX	Lung*	EX	Vagina	X	Skin
	Nose			EX	All gross lesions and masses*
	Pharynx				
	Larynx				

* Required for subchronic studies based on Subdivision F Guidelines
$^{+}$ Organ weight required in subchronic and chronic studies.
$^{++}$ Organ weight required for non-rodent studies.
^{T} = required only when toxicity or target organ

II. RESULTS

A. Observations :

1. Toxicity - No treatment-related changes in behaviour nor clinical signs of toxicity were noted during the study.

2. Mortality - One female rat treated at 1250 ppm was found dead on study day 57. Histopathological examination did not reveal any treatment-related findings, hence it was concluded that there was no treatment-related mortality in the study.

B. Body weight and weight gain: Mean body weight at week 13 was reduced in males at 1250, 2500 and 5000 ppm, with mean values 15%, 12% and 19% lower than controls, respectively. These correspond to reductions in body weight gain from initiation to week 13 of 22%, 19% and 27%. Body weight and body weight gain in males treated at 25 and 250 ppm, and in all treated females were not affected by treatment with CGA 293343 technical.

TABLE 2: Weekly male body weights

Dose (ppm)	0	25	250	1250	2500	5000
Males	Body weight (grams)					
Pretest	145.4	151.2	147.0	149.8	157.6	151.4
Week 1	204.4	209.1	202.0	202.5	211.7	195.4
Week 2	259.4	261.3	255.1	247.1	257.8	233.5-
Week 3	312.0	309.1	303.7	288.3-	298.6-	271.1*-
Week 4	348.4	345.1	338.6	316.5-	328.8-	297.8*-
Week 5	382.2	372.9	370.7	341.7-	350.8-	319.6*-
Week 6	417.6	401.2	400.3	365.7-	373.7-	341.6*-
Week 7	439.2	416.2	423.3	382.0-	391.9-	356.6*-
Week 8	464.6	434.5	445.0	398.6-	411.0-	371.4*-
Week 9	478.8	447.1	460.8	411.4-	425.1-	385.3*-
Week 10	494.5	461.1	476.7	422.5-	438.0-	399.6*-
Week 11	501.5	471.4	488.1	431.4	448.7-	412.7*-
Week 12	514.2	482.7	497.1	439.5	460.4-	421.9*-
Week 13	528.7	491.0	507.7	448.8-	467.6-	429.5*

Data obtained from page 68 of the study report.
* Significantly different from the control ($p < 0.01$), Lepage.
- Significant negative trend ($p < 0.01$), Jonckheere.

C. Food consumption and compound intake:

1. Food consumption - Overall mean food consumption (total, weeks -1 to 13) was reduced by 11%, 7% and 14% in males at 1250, 2500 and 5000 ppm, respectively. Food consumption was not affected in any of the other treated groups.

2. Compound consumption (time-weighted average): The mean daily intake of CGA 293343 technical, based on nominal concentrations in the diet were 1.719, 17.57, 85.8, 171.6 and 342.5 mg/kg bw/day in males and 1.853, 19.11, 93.5, 186.2 and 374.1 mg/kg bw/day in females. Corrected for analytically determined concentrations in the diet, the mean daily intake was 1.743, 17.64, 84.9, 167.8 and 328.8 mg/kg bw/day in males and 1.879, 19.19, 92.5, 182.1 and 359.1 mg/kg bw/day in females.

D. Water consumption: No statistically significant differences were reported, however the author considered the following changes to be related to treatment: a slight reduction in water intake in high

dose males during weeks 1-4; a slight increase in water intake in high dose males from week 7-13; and a slight increase in water consumption in high dose females from week 2 until the end of the study.

E. Ophthalmological examination: No abnormal findings were reported in any of the animals used in the study.

F. Blood work:

1. Haematology: Slightly increased platelet counts were observed in high dose males. No other treatment-related effects were reported.

2. Clinical Chemistry: Males receiving 1250, 2500 or 5000 had increased plasma creatinine and decreased glucose levels. High dose males also had increased plasma urea and cholesterol. Sodium and chloride levels were marginally decreased in males and females treated at 2500 or 5000 ppm. Males receiving 1250 also had marginally decreased chloride levels and males in the top two dose groups exhibited slightly increased phosphate levels. All other changes were considered to be unrelated to treatment with CGA 293343 technical. The marginal differences in electrolyte levels are all within the range of historical control values, and are of limited toxicological significance.

TABLE 3: Clinical chemistry findings

Dose (ppm)	0	25	250	1250	2500	5000
Males						
Creatinine (μmol/L)	52.88±4.34	55.77±2.73	54.98±4.05	60.65±6.38^{+}	59.03±6.31^{+}	64.28±5.87^{*+}
Glucose (mmol/L)	8.244±0.94	8.787±0.63	7.949±1.12	7.274±0.31^{*-}	7.530±0.85^{-}	7.205±1.18^{-}
Urea (mmol/L)	5.422±1.03	5.515±0.66	5.301±0.85	6.141±0.76	6.346±1.02	6.726±1.08^{+}
Cholesterol (mmol/L)	2.094±0.30	2.096±0.44	2.092±0.42	2.005±0.26	2.373±0.33	2.549±0.47^{+}
Sodium (mmol/L)	142.8±0.81	142.2±0.78	142.4±1.03	142.0±0.66	141.4±0.60^{*-}	142.1±1.43^{-}
Chloride (mmol/L)	100.6±1.13	101.1±0.86	100.4±2.22	98.96±1.11^{-}	98.24±1.90^{-}	98.73±1.79^{-}
Phosphate (mmol/L)	1.656±0.17	1.535±0.12	1.579±0.12	1.733±0.11	1.747±0.15^{+}	1.810±0.11^{+}
Females						
Sodium (mmol/L)	142.7±1.20	141.9±1.20	141.9±1.33	140.9±1.76	140.8±1.47^{-}	141.1±1.31^{-}
Chloride (mmol/L)	103.0±1.78	102.5±1.35	101.9±1.47	101.7±1.52	101.7±2.00^{-}	100.6±1.74^{-}

Data obtained from pages 116-120 of the study report.
* Significantly different from control ($p < 0.01$), Lepage.
$^{+/-}$ Significant positive or negative trend ($p < 0.01$), Jonckheere.

G. Urinalysis: No treatment-related effects were reported.

H. Sacrifice and Pathology:

1. Organ weight: Increased absolute adrenal weights were recorded in high dose males. The following organ to body weight ratios were also increased in high dose males: adrenal, heart, liver, kidney and spleen. Liver and kidney weights relative to body weight were also increased in males receiving 2500 ppm. Decreased absolute testis weight in high dose males was attributed to decreased body weight. Absolute heart and thymus weights were decreased in high dose females.

TABLE 4: Treatment-related changes in absolute and/or relative organ weights

Dose (ppm)	0	25	250	1250	2500	5000
Males						
Liver - relative to bw (%)	4.08	4.09	4.15	4.06	4.34	4.93*+
Kidney - relative to bw (%)	0.64	0.66	0.65	0.68	0.71	0.79*+
Adrenal - absolute (mg)	73.6	65.8	71.5	64.2	65.7	88.7
- relative to bw (%)	0.015	0.014	0.015	0.015	0.015	0.021*+
Heart- relative to bw (%)	0.28	0.29	0.28	0.32	0.30+	0.33*+
Spleen - relative to bw (%)	0.15	0.16	0.16	0.18	0.17+	0.19*+
Females						
Heart - absolute (g)	0.919	0.940	0.902	0.923	0.914	0.854-
Thymus - absolute (mg)	341.6	338.8	306.4	301.3	315.9	282.7

Data obtained from pages 136-138 of the study report.
* Significantly different from control ($p < 0.01$), Lepage.
+/- Significant positive or negative trend ($p < 0.01$), Jonckheere.

2. **Gross pathology:** No treatment-related findings were reported.

3. **Microscopic pathology:** Treatment-related changes are presented in Table 5.

Liver
Microscopic examination of liver tissue revealed a number of treatment-related changes, including hepatocellular hypertrophy, lymphohistiocytic infiltration of liver parenchyma, cholangiofibrosis of intrahepatic bile ducts and pigmentation of Kupffer cells. The changes that were deemed to be related to treatment with CGA 293343 were restricted to the top two dose groups.

Kidney
Increased incidence of hyaline change of renal tubular epithelium was noted in males at doses of 250 ppm and above. A progressive increase in the severity of this lesion was also observed in males (see table 5). The incidence of chronic tubular lesions was increased in males at doses of 250 ppm and above and in females at 2500 ppm and above. A dose-related increase in the incidence of acute tubular lesions and basophilic proliferation of renal tubules was observed in males at 1250 ppm and above. Renal pelvic dilatation was observed more frequently in males receiving 2500 ppm, and one male at 5000 ppm had marked dilatation of the renal pelvis. Cast formation was observed more frequently in high dose males. An increase in the severity of nephrocalcinosis was observed in females of the top two dose groups.

Adrenal gland
Fatty change was observed more frequently in males of the top three dose groups and in females of the top two dose groups.

Spleen
The author considered the observed increase in the incidence of hemosiderosis and extramedullary hematopoiesis in top dose males treatment-related. These findings occurred with similar frequency in the lower dose groups, and there is no clear dose-response, therefore it is unlikely that these are related to treatment with CGA 293343. The marginal increase in severity of hemosiderosis in females of the top two dose groups is probably related to treatment.

TABLE 5: Histopathology findings

Organ/observation	0 ppm	25 ppm	250 ppm	1250 ppm	2500 ppm	5000 ppm
Liver						
Hepatocellular hypertrophy (♂) mean severity	0 0	0 0	0 0	0 0	6 1.0	10 1.4
Hepatocellular hypertrophy (♀) mean severity	0 0	0 0	0 0	0 0	0 0	8 1.0
Lymphohistiocytic infiltration (♂) mean severity	3 1.0	4 1.3	6 1.2	5 1.0	4 1.3	9 1.2
Lymphohistiocytic infiltration (♀) mean severity	4 1.0	5 1.2	6 1.0	7 1.1	9 1.2	10 1.3
Cholangiofibrosis (♂) mean severity	2 1.0	4 1.0	2 1.0	4 1.3	5 1.0	6 1.0
Kupffer cell pigmentation (♀) mean severity	0 0	0 0	0 0	0 0	0 0	6 1.0
Kidney						
Hyaline change- tubular epithelium (♂) mean severity	1 1.0	0 0	4 1.3	8 1.5	10 1.7	10 2.3
Chronic tubular lesion (♂) mean severity	0 0	1 1.0	3 1.0	6 1.2	10 1.2	9 1.3
Chronic tubular lesion (♀) mean severity	4 1.0	5 1.0	7 1.3	7 1.0	9 1.4	10 1.4
Acute tubular lesion (♂) mean severity	0 0	0 0	0 0	3 1.6	8 1.5	9 2.1
Basophilic proliferation (♂) mean severity	2 1.0	1 1.0	2 1.0	4 1.3	6 1.0	10 1.6
Dilatation- renal pelvis (♂) mean severity	1 1.0	0 0	2 1.5	1 2.0	5 1.2	1 3.0
Cast formation (♂) mean severity	1 2.0	3 1.3	2 1.5	3 1.0	3 1.0	5 1.2
Nephrocalcinosis (♀) mean severity	10 1.6	10 1.8	10 1.9	10 1.7	10 2.4	10 2.5
Spleen						
Hemosiderosis (♂) mean severity	7 1.0	8 1.9	9 1.4	7 1.6	9 1.7	10 2.0
Hemosiderosis (♀) mean severity	9 1.7	10 2.3	10 2.1	10 1.9	10 2.6	10 2.7
Extramedullary hematopoiesis (♂) mean severity	3 1.0	2 1.0	3 1.0	5 1.0	2 1.0	5 1.8
Adrenal gland						
Fatty change (♂) mean severity	4 1.3	5 1.2	5 1.4	7 1.1	7 1.0	8 1.3
Fatty change (♀) mean severity	0 0	0 0	2 1.0	1 1.0	4 1.0	6 1.0

Data obtained from pages 46-47 of the study report.
Grading of lesions: 1 - minimal, 2 - moderate, 3 - marked.

III. DISCUSSION

A. A slight increase in the incidence of chronic lesions of the renal tubules was observed in females treated at 250 and 1250 ppm. At both of these doses, the incidence of this lesion was the same (7/10), however the mean severity was slightly greater at the lower dose. In the absence of a clear dose-response relationship, the incidence of this observation at these doses was regarded as a spurious effect, however it was considered to be treatment-related at 2500 and 5000 ppm. Chronic tubular lesions were observed in 9/10 and 10/10 females at 2500 and 5000 ppm, respectively, and an increase in the severity of nephrocalcinosis was observed.

The author stated that "the hyaline change in male kidneys consisted of eosinophilic droplets within the cytoplasm of proximal convoluted tubules as the result of an accumulation of alpha-2-microglobulin which is synthesized and secreted by the liver. This protein is normally present as eosinophilic granules within phagolysosomes in renal tubules of sexually mature male rats. One proposed mechanism of accumulation suggests the test article or a metabolite to bind with the protein or to alter the structure so that the tubular cell lysosomal enzymes cannot degrade the protein complex".

B. <u>**Study deficiencies**</u>: None

Author's conclusions: "Dietary administration of CGA 293343 tech. to albino rats at concentrations of 0, 25, 250, 1250, 2500 and 5000 ppm for 3 months resulted in:

- No adverse effects on survival
- No effect on appearance and behaviour
- A marked reduction in body weight gain in males only at 1250, 2500 and 5000 ppm
- A slight depression of the overall food intake in males at 1250, 2500 and 5000 ppm
- Slight changes to the mean water intake in males and females at 5000 ppm
- Slightly increased platelet counts in males at 5000 ppm and minimal changes to plasma creatinine, glucose, urea and cholesterol levels and to electrolyte concentrations at intermediate and high doses, but no effects on urine parameters
- Higher adrenal weight in high dose males and depressed testis weight associated with a retardation of body weight development and depressed carcass weight, and consequently, changes to organ to body weight ratios of most organs at 5000 ppm.
- Histopathological changes to liver, kidney, spleen and adrenal gland at intermediate and/or high dose levels

"A no-observable-effect level (NOEL) for males at 25 ppm (based on histopathologically observed changes in kidney) and for females at 1250 ppm, corresponding to mean daily intakes of 1.7 and 92.5 mg/kg body weight in males and females, respectively".

Reviewer's comments: Dietary administration of CGA 293343 technical to 10 Tif:RAIf (SPF) Sprague-Dawley rats per sex per group resulted in treatment-related changes in body weight and body weight gain, clinical biochemical parameters, absolute and relative organ weights and microscopic pathology of several tissues. The NOAEL from this study is 25 ppm for males and 1250 ppm for females, based on histopathological changes in the kidneys at 250 ppm and above in males and at 2500 ppm and above in females. These doses are equal to 1.74 and 92.5 mg/kg bw/day in males and females, respectively.

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R106488

Chemical:	**Thiamethoxam**
PC Code:	**060109**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/12/99**
File ID:	**00000000**
Accession Number:	**412-05-0094**

HED Records Reference Center
05/02/2005